NON-TECHNICAL ABSTRACT

A phase II, open-label, ascending-dose study of the safety and efficacy of Trinam™ (EG004) in stenosis prevention at the graft-vein anastomosis site in dialysis patients - Protocol 102

Patients who are having hemodialysis treatment for kidney disease often experience problems with the vascular access grafts required for dialysis. For hemodialysis access, a synthetic graft (an artificial piece of tubing) is placed by surgery into the arm of the patient with kidney disease which directly connects the arterial and venous systems. The graft can then be used for venipuncture to allow hemodialysis to occur. Unfortunately vascular accesses often fail because the graft-vein anastomosis (the site where the graft joins the vein) undergoes stenosis (narrowing) and the blood tends to clot. Approximately 40% of people with access grafts have problems with these grafts during the first 6 months after surgery. Stenosis occurs because the wall of the vein gets thicker than normal due to proliferation of smooth muscle cells (intimal hyperplasia) in the vein wall. Blood clots or stenosis of the vein can increase the risk of infection and the need for hospitalization to replace the graft. The hospital costs related to vascular access procedures in dialysis patients are estimated to be around $1.3 billion per year and the total cost of dialysis complications to the US healthcare system is thought to be in excess of $2 billion per year.

Ark Therapeutics Ltd is developing a biological product called Trinam based on gene transfer. The proposed indication for Trinam, is the prevention of intimal hyperplasia at the graft-vein anastomosis site in patients who require vascular access for hemodialysis due to kidney disease. The rationale for Trinam follows the discovery that vascular endothelial growth factor (VEGF) protects blood vessel walls from smooth muscle cell proliferation. This effect appears to be distinct from its more widely appreciated role in regulating growth and survival of blood vessels (1). Trinam consists of a gene for a type of VEGF (VEGF-D gene) that is taken up by smooth muscle cells in the vein wall to make a protein called VEGF-D which is believed to reduce the formation of intimal hyperplasia.

Trinam is applied at the time of surgery for the access graft. The surgeon will place a collagen tube or `collar' around the graft-vein anastomosis. A small amount of the VEGF-D gene solution is then placed between the outside of the vein and the collagen collar. The VEGF-D genes are carried into the vein wall by a virus called an adenovirus, similar to the common cold virus. Unlike the virus that causes the common cold, this virus has been changed so that it cannot multiply. This approach has already been tested in animal models. In rabbits, VEGF genes were found to prevent intimal hyperplasia of carotid arteries when administered using a silicon collar placed around the carotid artery (2).

The objective of the proposed study is to assess the effectiveness and safety of Trinam when applied to the graft-vein anastomosis site in patients with severe renal disease who require vascular access for dialysis. The study is a dose-escalation study, with the first cohort of eight patients to receive a dose of Trinam at 4×10^9 viral particles (replication-deficient adenoviral vector) at the time the graft is placed in the arm. There will be an independent safety review conducted after these eight patients are treated. Assuming a satisfactory safety review, a second cohort of eight patients will be treated with Trinam at 4×10^{10} viral particles. In addition, four patients will be recruited to the study as controls, and will undergo the standard graft placement but will receive no treatment. It is hypothesised that Trinam administration will result in less stenosis at the graft-vein anastomosis site compared with controls and therefore will reduce the need for treatment of thrombosis and stenosis in dialysis patients. All patients will be evaluated over 12 months. The highest dose of Trinam that might be administered in this study has already been tested in pigs and was not found to cause any significant side effects.

References:

1. Zachary I, Mathur A, Yla-Herttuala S. Vascular protection. A novel nonangiogenic cardiovascular role for vascular endothelial growth factor. *Arterioscler Thromb Vasc Biol* 2000;**20**:1512-1520.

2. Laitinen M, Zachary I, Breier G, et al. VEGF gene transfer reduces intimal thickening via increased production of nitric oxide in carotid arteries. *Hum Gen Ther* 1997;**8**:1737-1744.